Answer 1:

Bibliographic Information

Expression of t-DARPP Mediates Trastuzumab Resistance in Breast Cancer Cells. Belkhiri, Abbes; Dar, Altaf A.; Peng, Dun Fa; Razvi, Mohammad H.; Rinehart, Cammie; Arteaga, Carlos L.; El-Rifai, Wael. Authors' Affiliations: Departments of Surgery, Medicine, and Cancer Biology and Breast Cancer Research Program and Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Clinical Cancer Research (2008), 14(14), 4564-4571. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:855172 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: We have investigated the role of t-DARPP in trastuzumab resistance in ERBB2-amplified and overexpressed breast cancer cell lines. Exptl. Design: We have used the HR-5 and HR-6 trastuzumab-resistant cells that were established from tumors that recurred in the presence of trastuzumab therapy following xenografts of BT-474 cells in nude mice. In addn., SKBR-3 cells, engineered for stable expression of t-DARPP, and HCC-1569 cells, which have constitutive expression of t-DARPP and are de novo resistant to trastuzumab, were used. RESULTS: We reported ≥15-fold up-regulation of mRNA and protein levels of t-DARPP in HR-5 and HR-6 cells compared with their progenitor BT-474 trastuzumab-sensitive cells. The t-DARPP expression was not regulated by changes in its promoter DNA methylation levels. The SKBR-3 cells stably expressing t-DARPP developed resistance to trastuzumab compared with their parental cells and empty vector controls ($P < 0.01$). The trastuzumab-resistant cell lines showed a significant increase in pAKT (Ser473) and BCL2 protein levels. The small interfering RNA knockdown of t-DARPP in all trastuzumab-resistant cells led to a significant redn. in ERBB2, pAKT (Ser473), and BCL2 protein levels with a significant decrease in cell viability ($P \leq 0.001$) and an increase in cleaved caspase-3 levels, indicating the progression of these cells toward apoptosis. The t-DARPP protein was assocd. with both heat shock protein 90 and ERBB2 forming a potential protein complex. This assocn. may play a role in regulating ERBB2 protein in trastuzumab-resistant cells. CONCLUSION: We conclude that t-DARPP is a novel mol. target that can mediate the therapeutic resistance to trastuzumab in breast cancer cells.

Answer 2:

Bibliographic Information

Antitumor Efficacy of Trastuzumab in Nude Mice Orthotopically Xenografted With Human Pancreatic Tumor Cells Expressing Low Levels of HER-2/neu. Pratesi, Graziella; Petrangolini, Giovanna; Tortoreto, Monica; Addis, Alessandro; Zunino, Franco; Calcaterra, Claudia; Merlo, Andrea; Tagliabue, Elda; Menard, Sylvie; Balsari, Andrea. Preclinical Chemotherapy and Pharmacology Unit, University of Milan, Milan, Italy. Journal of Immunotherapy (2008), 31(6), 537-544. Publisher: Lippincott Williams & Wilkins, CODEN: JOIMF8 ISSN: 1524-9557. Journal written in English. AN 2008:776041 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The monoclonal antibody trastuzumab binds to the extracellular domain of HER-2/neu and induces clin. responses in breast tumors with HER-2 gene amplification and/or protein overexpression. Its role in other tumor types remains to be investigated. We evaluated the antitumor efficacy of trastuzumab in vitro and in nude mice implanted orthotopically with cells of 3 human pancreatic tumor lines expressing only low levels of HER-2/neu, as detd. by flow cytometry. Although none of the 3 cell lines showed growth inhibition when cultured directly with trastuzumab, 2 of them, GER and PaCa3, were sensitive to lysis in antibody-dependent cellular cytotoxicity assay. This pattern of response was recapitulated in tumor-bearing mice repeatedly treated with trastuzumab, in which survival was significantly prolonged as compared with controls ($P=0.03$ for GER and 0.0008 for PaCa3). Incidence of metastases was also reduced, esp. in liver. These preclin. results indicate that trastuzumab can exert an antitumor effect against orthotopic human pancreatic cancer xenografts with low-level HER-2/neu expression and that this effect correlates with the in vitro antibody-dependent cellular cytotoxicity susceptibility, suggesting a different role for HER-2/neu in the therapy of tumor types other than breast cancer.

Answer 3:

Bibliographic Information

PAMAM dendrimer-based contrast agents for MR imaging of Her-2/neu receptors by a three-step pretargeting approach. Zhu, Wenlian; Okollie, Baasil; Bhujwalla, Zaver M.; Artemov, Dmitri. JHU ICMIC Program, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Magnetic Resonance in Medicine (2008), 59(4), 679-685. Publisher: Wiley-Liss, Inc., CODEN: MRMEEN ISSN: 0740-3194. Journal written in English. AN 2008:514983 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pretargeting of receptors is a useful approach in mol. imaging and therapy to reduce background noise or toxicity and enhance selectivity. In this study a three-step pretargeting approach that includes a biotinylated antibody, avidin/streptavidin, and a biotinylated imaging agent is described. A PAMAM dendrimer generation 4 (G4D)-based MRI T1 agent biotin-G4D-DTPA-Gd (bG4D-Gd) and its sister compd. with remaining free surface amine groups blocked by succinic anhydride to reduce pos. charges (bG4D-Gd-SA) were synthesized. Limited selective enhancement in MRI was obsd. in a Her-2/neu mouse tumor xenograft by this three-step pretargeting approach that includes biotinylated trastuzumab, avidin and bG4D-Gd, or bG4D-Gd-SA. However, these dendrimer-based MRI agents with mol. wt. around 29 kD reached and remained in the tumor through the enhanced permeability and retention effect. Prolonged and extensive accumulation of both bG4D-Gd and b-G4-Gd-SA in the kidneys was also obsd.

Answer 4:

Bibliographic Information

Direct Visualization of Heterogeneous Extravascular Distribution of Trastuzumab in Human Epidermal Growth Factor Receptor Type 2 Overexpressing Xenografts. Baker, Jennifer H. E.; Lindquist, Kirstin E.; Huxham, Lynsey A.; Kyle, Alastair H.; Sy, Jonathan T.; Minchinton, Andrew I. Authors' Affiliation: Medical Biophysics Department, British Columbia Cancer Research Center, Vancouver, BC, Can. Clinical Cancer Research (2008), 14(7), 2171-2179. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:422802 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The high mol. wt. and binding affinity of trastuzumab, a monoclonal antibody in use for treatment of breast cancers overexpressing human epidermal growth factor receptor type 2 (HER2), in combination with microenvironmental factors, may limit its distribution and efficacy. We assessed and mapped the distribution of systemically given, unlabeled trastuzumab at micrometer resoln. in tumor xenografts using immunohistochem. Exptl. Design: Mice bearing MDA-435/LCC6HER2 xenografts were given single doses of 4 or 20 mg/kg unlabeled trastuzumab with tumor harvest at various time points thereafter; bound trastuzumab was imaged directly in tumor cryosections using fluorescently tagged antihuman secondary antibodies. Combinations of addnl. markers, including HER2, 5-bromo-2-deoxyuridine, CD31, DioC7(3), desmin, and collagen IV were also mapped on the same tumor sections. RESULTS: Distribution of trastuzumab in MDA-435/LCC6HER2 tumors is found to be heterogeneous, with tumor margins satg. more thoroughly in doses and times analyzed. Considerable intervessel heterogeneity is also seen. For example, in unsatd. tissues, there remain perfused vessels without any trastuzumab in addn. to vessels with a few layers of pos. stained perivascular cells, in addn. to vessels with bound drug up to 150 μm away. This heterogeneity is independent of HER2 expression, microvessel d., and perfusion. A slightly greater proportion of vessels were assocd. with pericytes in sections with greater trastuzumab satn., but this would not adequately account for obsd. heterogeneous trastuzumab distribution. CONCLUSIONS: Complete penetration of trastuzumab in tumor tissue was not seen in our study, leaving the possibility that inadequate distribution may represent a mechanism for resistance to trastuzumab.

Answer 5:

Bibliographic Information

In vivo monitoring of a fluorescently labeled antibody in mice with breast cancer xenografts. Black, Robert D.; Bolick, Natasha G.; Richardson, Rachel A.; Dewhirst, Mark W. Sicel Technologies, Inc., Morrisville, NC, USA. IEEE Sensors Journal (2008), 8(1), 81-88. Publisher: Institute of Electrical and Electronics Engineers, CODEN: ISJEAZ ISSN: 1530-437X. Journal written in English. CAN 148:583650 AN 2008:263190 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Following the uptake kinetics of a monoclonal antibody cancer therapy in vivo is addressed in this study via the use of a surface probe to assay a fluorescent label attached to the antibody. Female NCr-nu athymic mice were implanted with cells from a human breast cancer MCF7HER2 line that over expresses clin. relevant levels of the HER2/neu protein. Herceptin (trastuzumab) and a neg. control antibody for mouse IgG Ab-1 were labeled with Alexa Fluor 647 fluorescent dye and the mice received a single bolus injection (tail vein) of one of the two antibodies. The relative signal in the tumor region was compared with that from normal tissue and a ratio of the signal levels was recorded as a function of time. As expected, Herceptin was found to conc. in the HER2+ tumors (high tumor-to-normal ratio), whereas the tumor-to-normal ratio for the neg. control antibody was flat in time and close to unity. It is suggested that fluorescence assays of this type might be possible in vivo in humans using a telemetric, implantable version of the probe used in this study.

Answer 6:

Bibliographic Information

A Novel Raji-Burkitt's Lymphoma Model for Preclinical and Mechanistic Evaluation of CD52-Targeted Immunotherapeutic Agents. Lapalombella, Rosa; Zhao, Xiaobin; Triantafillou, Georgia; Yu, Bo; Jin, Yan; Lozanski, Gerard; Cheney, Carolyn; Heerema, Nyla; Jarjoura, David; Lehman, Amy; Lee, L. James; Marcucci, Guido; Lee, Robert J.; Caligiuri, Michael A.; Muthusamy, Natarajan; Byrd, John C. Division of Hematology-Oncology, The Ohio State University, Columbus, OH, USA. Clinical Cancer Research (2008), 14(2), 569-578. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:126265 AN 2008:106236 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: To date, efforts to study CD52-targeted therapies, such as alemtuzumab, have been limited due to the lack of stable CD52 expressing transformed B-cell lines and animal models. We describe generation and utilization of cell lines that stably express CD52 both in vitro and in vivo. Exptl. Design: By limiting diln., we have established several clones of Raji-Burkitt's lymphoma cell line that express surface CD52. Immunophenotype and cytogenetic characterization of these clones was done. In vivo usefulness of the CD52high cell line to evaluate the therapeutic efficacy of CD52-directed antibody was investigated using a SCID mouse xenograft model. RESULTS: Stable expression of CD52 was confirmed in cells cultured in vitro up to 52 wk of continuous growth. The functional integrity of the expressed CD52 mol. was shown using alemtuzumab, which induced cytotoxic effects in vitro in the CD52high but not the CD52low clone. Compared with control antibody, alemtuzumab treatment in CD52high inoculated mice resulted in significantly increased median survival. Comparable levels of CD52-targeted direct cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity and anti-CD52 immunoliposome-mediated delivery of synthetic oligodeoxyribo nucleotides in CD52high clone and primary B-chronic lymphocytic leukemia cells implicated potential in vivo application of this model for evaluation of CD52-targeted antibody and immunoliposomes encapsulating therapeutic agents. CONCLUSIONS: These results show the in vitro utility of the cloned Raji cell lines that stably express high levels CD52. The disseminated leukemia-lymphoma mouse model described herein using these stable cell lines can serve as an excellent system for in vivo therapeutic and mechanistic evaluation of existing and novel antibodies directed against CD52 mol.

Answer 7:

Bibliographic Information

Trastuzumab decreases the number of circulating and disseminated tumor cells despite trastuzumab resistance of the primary tumor. Barok, Mark; Balazs, Margit; Nagy, Peter; Rakosy, Zsuzsa; Treszl, Andrea; Toth, Eniko; Juhasz, Istvan; Park, John

W.; Isola, Jorma; Vereb, Gyoergy; Szollosi, Janos. Department of Biophysics and Cell Biology, University of Debrecen, Debrecen, Hung. Cancer Letters (Amsterdam, Netherlands) (2008), 260(1-2), 198-208. Publisher: Elsevier B.V., CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 148:535809 AN 2008:85297 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have recently shown that despite of the fact that the ErbB2-pos. JIMT-1 human breast cancer cells intrinsically resistant to trastuzumab in vitro, trastuzumab inhibited the outgrowth of early phase JIMT-1 xenografts in SCID mice via antibody-dependent cellular cytotoxicity (ADCC). Here we show that trastuzumab significantly reduces the no. of circulating and disseminated tumor cells (CTCs and DTCs) in this xenograft model system at a time when the primary tumor is already unresponsive to trastuzumab. This observation suggests that ErbB2 pos. CTCs and DTCs might be sensitive to trastuzumab-mediated ADCC even if when the primary tumor is already non-responsive. Thus, trastuzumab treatment might also be beneficial in the case of patients with breast cancer that is already trastuzumab resistant.

Answer 8:

Bibliographic Information

Hyaluronan-induced masking of ErbB2 and CD44-enhanced trastuzumab internalization in trastuzumab resistant breast cancer. Palyi-Krekk, Zsuzsanna; Barok, Mark; Isola, Jorma; Tammi, Markku; Szoellosi, Janos; Nagy, Peter. Department of Biophysics and Cell Biology, Medical and Health Science Centre, University of Debrecen, Debrecen, Hung. European Journal of Cancer (2007), 43(16), 2423-2433. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 148:345900 AN 2007:1227802 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although trastuzumab, a recombinant humanized anti-ErbB2 antibody, is widely used in the treatment of breast cancer, neither its mechanism of action, nor the factors leading to resistance are fully understood. We have previously shown that antibody-dependent cellular cytotoxicity is pivotal in the in vivo effect of trastuzumab against JIMT-1, a cell line showing in vitro resistance to the antibody, and suggested that masking of the trastuzumab-binding epitope by MUC-4, a cell surface mucin, took place. Here, we further explored the role of masking of ErbB2 in connection with CD44 expression and synthesis of its ligand, hyaluronan. We show that high expression of CD44 obsd. in JIMT-1 cells correlates with ErbB2 downregulation in vivo, while siRNA-mediated inhibition of CD44 expression leads to decreased rate of trastuzumab internalization and low cell proliferation in vitro. An inhibitor of hyaluronan synthesis, 4-methylumbelliferon (4-MU) significantly reduced the hyaluronan level of JIMT-1 cells both in vivo and in vitro leading to enhanced binding of trastuzumab to ErbB2 and increased ErbB2 down-regulation. Furthermore, the inhibitory effect of trastuzumab on the growth of JIMT-1 xenografts was significantly increased by 4-MU treatment. Our results point to the importance of the CD44-hyaluronan pathway in the escape of tumor cells from receptor-oriented therapy.

Answer 9:

Bibliographic Information

Dual-labeled trastuzumab-based imaging agent for the detection of human epidermal growth factor receptor 2 overexpression in breast cancer. Sampath, Lakshmi; Kwon, Sunkuk; Ke, Shi; Wang, Wei; Schiff, Rachel; Mawad, Michel E.; Sevick-Muraca, Eva M. Division of Molecular Imaging, Department of Radiology, Baylor College of Medicine, Houston, TX, USA. Journal of Nuclear Medicine (2007), 48(9), 1501-1510. Publisher: Society of Nuclear Medicine, CODEN: JNMEAQ ISSN: 0161-5505. Journal written in English. CAN 148:372907 AN 2007:1153268 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of the human epidermal growth factor receptor (HER) family has been implicated in cancer because of its participation in signaling pathways regulating cellular proliferation, differentiation, motility, and survival. In this work, we exploited the extracellular

binding property of trastuzumab, a clin. therapeutic monoclonal antibody to the second member of the HER family (HER2), to design a diagnostic imaging agent, (111In-DTPA)n-trastuzumab-(IRDye 800CW)m, that is dual labeled with 111In, a γ-emitter, and a near-IR (NIR) fluorescent dye, IRDye 800CW, to detect HER2 overexpression in breast cancer cells. The stoichiometric ratios "n" and "m" refer to the no. of diethylenetriaminepentaacetic acid dianhydride (DTPA) and IRDye 800CW mols. bound per trastuzumab mol., resp. Methods: Fluorescence microscopy and confocal microscopy were used to det. the mol. specificity of (DTPA)n-trastuzumab-(IRDye800)m in vitro in SKBr3 (HER2-pos.) and MDA-MB-231 (HER2-neg.) breast cancer cells. SKBr3 cells were incubated with (DTPA)n-trastuzumab-(IRDye800)m or IRDye800CW or pretreated with trastuzumab or human IgG followed by (DTPA)n-trastuzumab-(IRDye800)m and examd. under a fluorescence microscope. For in vivo characterization, athymic nude mice bearing HER2-overexpressing SKBr3-luc s.c. xenografts were injected i.v. with (111In-DTPA)n-trastuzumab-(IRDye800)m and imaged with SPECT and NIR fluorescence imaging at 48 h. Tumor-bearing mice were also injected i.v. with trastuzumab 24 h before administration of (111In-DTPA)n-trastuzumab-(IRDye800)m. Nonspecific uptake in the SKBr3-luc tumors was analyzed by injecting the mice with IRDye 800CW and (111In-DTPA)p-IgG-(IRDye800)q, where "p" and "q" are the stoichiometric ratios of DTPA and IRDye 800CW bound per IgG antibody, resp. Results: (DTPA)n-trastuzumab-(IRDye800)m showed significantly greater binding to SKBr3 cells than to MDA-MB-231 cells. Confocal imaging revealed that this binding occurred predominantly around the cell membrane. Competitive binding studies with excess trastuzumab before incubation with (DTPA)n-trastuzumab-(IRDye800)m abolished this binding affinity, but pretreatment with nonspecific IgG did not alter binding. In vivo nuclear and optical imaging of SKBr3-luc xenografts injected with (111In-DTPA)n-trastuzumab-(IRDye800)m revealed significantly more uptake in the tumor region than in the contralateral muscle region. The tumor-to-muscle ratio decreased in mice pretreated with trastuzumab and in mice injected with IRDye 800CW and (111In-DTPA)p-IgG-(IRDye800)q. Ex vivo imaging of dissected organs confirmed these results. Finally, coregistration of histol. hematoxylin-eosin stains with autoradiog. signals from tumor and muscle tissue slices indicated that (111In-DTPA)n-trastuzumab-(IRDye800)m bound only in tumor tissue and not to muscle. Conclusion: Dual-labeled (111In-DTPA)n-trastuzumab-(IRDye800)m may be an effective diagnostic biomarker capable of tracking HER2 overexpression in breast cancer patients.

Answer 10:

Bibliographic Information

Preclinical Testing of Clinically Applicable Strategies for Overcoming Trastuzumab Resistance Caused by PTEN Deficiency. Lu, Chien-Hsing; Wyszomierski, Shannon L.; Tseng, Ling-Ming; Sun, Meng-Hong; Lan, Keng-Hsueh; Neal, Christopher L.; Mills, Gordon B.; Hortobagyi, Gabriel N.; Esteva, Francisco J.; Yu, Dihua. Department of Molecular and Cellular Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2007), 13(19), 5883-5888. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:205502 AN 2007:1104655 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: We have previously shown that PTEN loss confers trastuzumab resistance in ErbB2-overexpressing breast cancer using cell culture, xenograft models, and patient samples. This is a crit. clin. problem because trastuzumab is used in a variety of therapeutic regimens, and at the current time, there are no established clin. strategies to overcome trastuzumab resistance. Here, we did preclin. studies on the efficacy of clin. applicable inhibitors of the Akt/mammalian target of rapamycin (mTOR) pathway to restore trastuzumab sensitivity to PTEN-deficient cells. Exptl. Design: Cell culture and xenograft models were used to test a panel of clin. applicable, small-mol. inhibitors of the Akt/mTOR signal transduction pathway, a crit. pathway downstream of ErbB2, and identify compds. with the ability to restore trastuzumab sensitivity to PTEN-deficient cells. RESULTS: When trastuzumab was combined with the Akt inhibitor triciribine, breast cancer cell growth was inhibited and apoptosis was induced. In a xenograft model, combination therapy with trastuzumab and triciribine dramatically inhibited tumor growth. The combination of trastuzumab and the mTOR inhibitor RAD001 also slowed breast cancer cell growth in vitro and in vivo. CONCLUSIONS: Combining trastuzumab with inhibitors of the Akt/mTOR pathway is a clin. applicable strategy and combinations of trastuzumab with triciribine or RAD001 are promising regimens for rescue of trastuzumab resistance caused by PTEN loss.

Answer 11:

Bibliographic Information

Antitumor activity of capecitabine and bevacizumab combination in a human estrogen receptor-negative breast adenocarcinoma xenograft model. Higgins, Brian; Kolinsky, Kenneth; Linn, Michael; Adames, Violeta; Zhang, Yu-E.; Moisa, Carlos; Dugan, Ute; Heimbrook, David; Packman, Kathryn. Department of Discovery Oncology, Hoffmann-La Roche Inc., Nutley, NJ, USA. Anticancer Research (2007), 27(4B), 2279-2287. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 147:439706 AN 2007:994186 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Capecitabine and bevacizumab have each been shown to inhibit tumor growth. Their combination failed to improve survival in a phase III trial of metastatic breast cancer (MBC), although it should be noted patients had been heavily pretreated with anthracyclines and taxanes. Our aim was to evaluate whether combination treatment would increase tumor growth inhibition and survival in a breast cancer model. Materials and Methods: Mice bearing KPL-4 human estrogen receptor-neg. breast adenocarcinoma xenografts were given capecitabine orally daily for 14 days at the max. tolerated dose (MTD) or half MTD, alone or with 5 mg/kg i.p. bevacizumab twice weekly. Results: Tumor growth inhibition (TGI) and increased life span (ILS) were superior in the combination groups vs. monotherapy ($p<0.05$). TGI and ILS were significantly improved in the high- vs. low-dose capecitabine combination ($p<0.05$). Conclusion: Capecitabine in combination with bevacizumab provides a basis for pursuing the combination for first-line treatment of MBC.

Answer 12:

Bibliographic Information

Antitumor activity of a combination of trastuzumab (Herceptin) and oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2-overexpressing pancreatic cancer. Saeki, Hiroyuki; Yanoma, Shunsuke; Takemiya, Shouji; Sugimasa, Yukio; Akaike, Makoto; Yukawa, Norio; Rino, Yasushi; Imada, Toshio. Department of General Surgery, Yokohama City University, 3-9 Hukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan. Oncology Reports (2007), 18(2), 433-439. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 147:398030 AN 2007:955678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effect of trastuzumab in combination with oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2 (HER2)-overexpressing human pancreatic cancer cell line TRG in vitro and in vivo was investigated. HER2 expression in TRG was analyzed by RT-PCR and flow cytometry. For in vitro expts., 5-fluorouracil (5-FU) was used instead of S-1. In vivo studies were conducted with TRG xenografts in athymic mice. Trastuzumab (10 mg/kg) was administered i.p. once a week for 4 wk. S-1 (10 mg/kg) was administered orally 5 days a week for 4 wk. The results showed that TRG cells were pos. for HER2 mRNA and overexpressed HER2 protein. Either trastuzumab or 5-FU concn.-dependently inhibited the growth of TRG cells. The combination of trastuzumab and 5-FU resulted in a significant inhibition of growth of TRG cells compared to either agent alone ($P<0.001$). Incubation of TRG cells with peripheral blood mononuclear cells after treatment with trastuzumab enhanced the antiproliferative effect of trastuzumab, which could be the result of antibody-dependent cellular cytotoxicity. The combination of trastuzumab and S-1 resulted in a significant redn. in xenograft vol. compared to each agent alone ($P<0.0001$). In conclusion, this study showed that combination therapy with trastuzumab and S-1 may be effective for HER2-overexpressing pancreatic cancer patients.

Answer 13:

Bibliographic Information

Human breast cancer cells selected for resistance to trastuzumab in vivo overexpress epidermal growth factor receptor and ErbB ligands and remain dependent on the ErbB receptor network. Ritter, Christoph A.; Perez-Torres, Marianela; Rinehart, Cammie; Guix, Marta; Dugger, Teresa; Engelman, Jeffrey A.; Arteaga, Carlos L. Institute of Pharmacology and Institute of Pharmacy, University of Greifswald, Greifswald, Germany. Clinical Cancer Research (2007), 13(16), 4909-4919. Publisher:

American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:205417 AN 2007:905566 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have investigated mechanisms of acquired resistance to the HER2 antibody trastuzumab in BT-474 human breast cancer cells. BT-474 xenografts established in athymic nude mice were eliminated by trastuzumab. Continuous cell lines (HR for Herceptin resistant) were generated from tumors that recurred in the presence of continuous antibody therapy. The isolated cells behaved resistant to trastuzumab in culture as well as when reinjected into nude mice. They retained HER2 gene amplification and trastuzumab binding and were exquisitely sensitive to peripheral blood mononuclear cells ex vivo in the presence of the antibody. The HR cells exhibited higher levels of phosphorylated epidermal growth factor receptor (EGFR) and EGFR/HER2 heterodimers. Phosphorylation of HER2 in HR cells was inhibited by the EGFR tyrosine kinase inhibitors erlotinib and gefitinib. Gefitinib also inhibited the basal assocn. of p85 with phosphorylated HER3 in HR cells. Both inhibitors as well as the dual EGFR/HER2 inhibitor, lapatinib, induced apoptosis of the HR cells in culture. Growth of established HR5 xenografts was inhibited by erlotinib in vivo. In addn., the HR cells overexpressed EGFR, transforming growth factor α, heparin-binding EGF, and heregulin RNAs compared with the parental trastuzumab-sensitive cells. These results are consistent with the inability of trastuzumab to block the heterodimerization of HER2 and suggest that amplification of ligand-induced activation of ErbB receptors is a plausible mechanism of acquired resistance to trastuzumab that should be investigated in primary mammary cancers.

Answer 14:

Bibliographic Information

Trastuzumab causes antibody-dependent cellular cytotoxicity-mediated growth inhibition of submacroscopic JIMT-1 breast cancer xenografts despite intrinsic drug resistance. Barok, Mark; Isola, Jorma; Palyi-Krekk, Zsuzsanna; Nagy, Peter; Juhasz, Istvan; Vereb, Gyoergy; Kauraniemi, Paeivikki; Kapanen, Anita; Tanner, Minna; Vereb, Gyoergy; Szoelloesi, Janos. Departments of Biophysics and Cell Biology, Dermatology, Medical Chemistry, Cell Biology and Signaling Research Group, Hungarian Academy of Sciences, University of Debrecen, Debrecen, Hung. Molecular Cancer Therapeutics (2007), 6(7), 2065-2072. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:268447 AN 2007:749013 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Trastuzumab is a recombinant antibody drug that is widely used for the treatment of breast cancer. Despite encouraging clin. results, some cancers are primarily resistant to trastuzumab, and a majority of those initially responding become resistant during prolonged treatment. The mechanisms of trastuzumab resistance have not been fully understood. The authors examd. the role of antibody-dependent cellular cytotoxicity (ADCC) using JIMT-1 cells that are ErbB2 pos. but intrinsically resistant to trastuzumab in vitro. Unexpectedly, in expts. mimicking adjuvant therapy of submacroscopic disease in vivo (JIMT-1 cells inoculated s.c. in severe combined immunodeficiency mice), trastuzumab was able to inhibit the outgrowth of macroscopically detectable xenograft tumors for up to 5-7 wk. The effect is likely to be mediated via ADCC because trastuzumab-F(ab')2 was ineffective in this model. Moreover, in vitro ADCC reaction of human leukocytes was equally strong against breast cancer cells intrinsically sensitive (SKBR-3) or resistant (JIMT-1) to trastuzumab or even against a subline of JIMT-1 that was established from xenograft tumors growing despite trastuzumab treatment. These results suggest that ADCC may be the predominant mechanism of trastuzumab action on submacroscopic tumor spread. Thus, measuring the ADCC activity of patient's leukocytes against the tumor cells may be a relevant predictor of clin. trastuzumab responsiveness in vivo.

Answer 15:

Bibliographic Information

A New Model of Patient Tumor-Derived Breast Cancer Xenografts for Preclinical Assays. Marangoni, Elisabetta; Vincent-Salomon, Anne; Auger, Nathalie; Degeorges, Armelle; Assayag, Franck; de Cremoux, Patricia; de Plater, Ludmilla; Guyader,

Charlotte; De Pinieux, Gonzague; Judde, Jean-Gabriel; Rebucci, Magali; Tran-Perennou, Carine; Sastre-Garau, Xavier; Sigal-Zafrani, Brigitte; Delattre, Olivier; Dieras, Veronique; Poupon, Marie-France. U612, Pharmacologie Preclinique Antitumorale, Institut National de la Sante et de la Recherche Medicale, Fr. Clinical Cancer Research (2007), 13(13), 3989-3998. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:397725 AN 2007:718559 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: To establish a panel of human breast cancer (HBC) xenografts in immunodeficient mice suitable for pharmacol. preclin. assays. Exptl. Design: 200 samples of HBCs were grafted into Swiss nude mice. Twenty-five transplantable xenografts were established (12.5%). Their characterization included histol., p53 status, genetic anal. by array comparative genomic hybridization, gene expression by Western blotting, and quant. reverse transcription-PCR. Biol. profiles of nine xenografts were compared with those of the corresponding patient's tumor. Chemosensitivities of 17 xenografts to a combination of Adriamycin and cyclophosphamide (AC), docetaxel, trastuzumab, and Degarelix were evaluated. RESULTS: Almost all patient tumors established as xenografts displayed an aggressive phenotype, i.e., high-grade, triple-neg. status. The histol. of the xenografts recapitulated the features of the original tumors. Mutation of p53 and inactivation of Rb and PTEN proteins were found in 83%, 30%, and 42% of HBC xenografts, resp. Two HBCx had an ERBB2 (HER2) amplification. Large variations were obsd. in the expression of HER family receptors and in genomic profiles. Genomic alterations were close to those of original samples in paired tumors. Three xenografts formed lung metastases. A total of 15 of the 17 HBCx (88%) responded to AC, and 8 (47%) responded to docetaxel. One ERBB2-amplified xenograft responded to trastuzumab, whereas the other did not. The drug response of HBC xenografts was concordant with that of the patient's tumor in five of seven analyzable cases. CONCLUSIONS: This panel of breast cancer xenografts includes 15 triple-neg., one ER pos. and 2 ERBB2 pos. This panel represents a useful preclin. tool for testing new agents and protocols and for further exploration of the biol. basis of drug responses.

Answer 16:

Bibliographic Information

Anti-tumor effect of anti-HER-2 engineering antibodies Herceptin and chA21 on nude mice xenografts of human ovarian cancer SKOV3 cells. Ling, Xiaoguang; Wu, Qiang; Xue, Hua; Yang, Feng; Cheng, Liansheng; Liu, Jing. Department of Pathology, Anhui Medical University, Hefei, Anhui Province, Peop. Rep. China. Xi'an Jiaotong Daxue Xuebao, Yixueban (2006), 27(2), 109-112, 131. Publisher: XiÏan Jiaotong Daxue Xuebao, Yixueban Bianjibu, CODEN: XJDXAS ISSN: 1671-8259. Journal written in Chinese. CAN 148:8774 AN 2007:711166 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

It was studied that the anti-tumor effect of anti-HER-2 engineering antibodies chA21 and Herceptin on nude mice xenografts of human ovarian cancer SKOV3 cells and its mechanism. An animal model with human ovarian cancer SKOV3 cells involved in nude mice was established and the mice were randomized into 3 groups: normal saline (NS), chA21 and Herceptin. The mice were resp. administrated with Herceptin (30 mg/kg) and chA21 (30 mg/kg) via caudal vein injection twice a week for consecutive 6 wk, and then were killed after 44 days administration of the drugs. The vols. of the xenografts were measured twice a week. The tumor wt. and inhibition ratio were measured after mice were killed. Ki-67 and NFκB expression in the three groups was quantificationally analyzed by immunohistochem. on tissue microarray sections combined with a micro-image analyzing system. The growth of xenografts of human ovarian cancer SKOV3 cells in nude mice was significantly inhibited by either Herceptin or chA21. Both Ki-67 labeling indexes and NFκB levels in chA21 and Herceptin groups were lower than those in the control ($P<0.01$). Herceptin and chA21 may inhibit the growth of transplantations of human ovarian cancer SKOV3 cells. Down-regulation of NFκB expression in SKOV3 cells might be one of their possible mechanisms.

Answer 17:

Bibliographic Information

Treatment of human epidermal growth factor receptor 2-overexpressing breast cancer xenografts with multiagent HER-targeted therapy. Arpino, Grazia; Gutierrez, Carolina; Weiss, Heidi; Rimawi, Mothaffar; Massarweh, Suleiman; Bharwani, Lavina; De Placido, Sabino; Osborne, C. Kent; Schiff, Rachel. Breast Center and the Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA. Journal of the National Cancer Institute (2007), 99(9), 694-705. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 148:393927 AN 2007:652807 CAPLUS

Abstract

Human epidermal growth factor receptor 2 (HER2) is a member of the HER signaling pathway. HER inhibitors partially block HER signaling and tumor growth in preclin. breast cancer models. We investigated whether blockade of all HER homo- and heterodimer pairs by combined treatment with several inhibitors could more effectively inhibit tumor growth in such models. Mice carrying xenograft tumors of HER2-overexpressing MCF7/HER2-18 (HER2-transfected) or BT474 (HER2-amplified) cells were treated with estrogen supplementation or estrogen withdrawal, alone or combined with tamoxifen. One to three HER inhibitors (pertuzumab, trastuzumab, or gefitinib) could also be added ($n \geq 8$ mice per group). Tumor vols., HER signaling, and tumor cell proliferation and apoptosis were assessed. Results were analyzed with the t test or Wilcoxon rank sum test and survival anal. methods. All statistical tests were two-sided. Median time to tumor progression was 21 days for mice receiving estrogen and 28 days for mice receiving estrogen and pertuzumab (difference = 7 days; P = .001; hazard ratio [HR] of progression in mice receiving estrogen and pertuzumab vs. mice receiving estrogen = 0.27, 95% confidence interval [CI] = 0.09 to 0.77). Addn. of gefitinib and trastuzumab to estrogen and pertuzumab increased this time to 49 days (difference = 21 days; P = .004; HR of progression = 0.28, 95% CI = 0.10 to 0.76). MCF7/HER2-18 tumors disappeared completely and did not progress (for ≥189 days) after combination treatment with pertuzumab, trastuzumab, and gefitinib plus tamoxifen (19 of 20 mice) or plus estrogen withdrawal (14 of 15 mice). Both combination treatments induced apoptosis and blocked HER signaling and proliferation in tumor cells better than any single agent or dual combination. All BT474 tumors treated with pertuzumab, trastuzumab, and gefitinib disappeared rapidly, regardless of endocrine therapy, and no tumor progression was obsd. for 232 days.

Combined treatment with gefitinib, trastuzumab, and pertuzumab to block signals from all HER homo- and heterodimers inhibited growth of HER2-overexpressing xenografts statistically significantly better than single agents and dual combinations.

Answer 18:

Bibliographic Information

In vivo Therapeutic Synergism of Anti-Epidermal Growth Factor Receptor and Anti-HER2 Monoclonal Antibodies against Pancreatic Carcinomas. Larbouret, Christel; Robert, Bruno; Navarro-Teulon, Isabelle; Thezenas, Simon; Ladjemi, Maha-Zohra; Morisseau, Sebastien; Campigna, Emmanuelle; Bibeau, Frederic; Mach, Jean-Pierre; Pelegrin, Andre; Azria, David. Institut National de la Sante et de la Reserche Medicale, EMI 0227, Centre de Recherche en cancerologie de Montpellier, Universite Montpellier I, Montpellier, Fr. Clinical Cancer Research (2007), 13(11), 3356-3362. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:404256 AN 2007:602103 CAPLUS

Abstract

PURPOSE: Pancreatic carcinoma is highly resistant to therapy. Epidermal growth factor receptor (EGFR) and HER2 have been reported to be both dysregulated in this cancer. To evaluate the in vivo effect of binding both EGFR and HER2 with two therapeutic humanized monoclonal antibodies (mAb), we treated human pancreatic carcinoma xenografts, expressing high EGFR and low HER2 levels. Exptl. Design: Nude mice, bearing xenografts of BxPC-3 or MiaPaCa-2 human pancreatic carcinoma cell lines, were injected twice weekly for 4 wk with different doses of anti-EGFR (matuzumab) and anti-HER2 (trastuzumab) mAbs either alone or in combination. The effect of the two mAbs, on HER receptor phosphorylation, was also studied in vitro by Western blot anal. RESULTS: The combined mAb treatment significantly inhibited tumor progression of the BxPC-3 xenografts compared with single mAb injection (P = 0.006) or no treatment (P = 0.0004) and specifically induced some complete remissions. The two mAbs had more antitumor effect than 4-fold greater doses of each mAb. The significant synergistic effect of the two mAbs was confirmed on the MiaPaCa-2 xenograft and on another type of carcinoma, SK-OV-3 ovarian carcinoma xenografts. In vitro, the cooperative effect of

the two mAbs was assocd. with a decrease in EGFR and HER2 receptor phosphorylation. CONCLUSIONS: Anti-HER2 mAb has a synergistic therapeutic effect when combined with an anti-EGFR mAb on pancreatic carcinomas with low HER2 expression. These observations may open the way to the use of these two mAbs in a large panel of carcinomas expressing different levels of the two HER receptors.

Answer 19:

Bibliographic Information

Potentiation of antitumor activity of docetaxel by combination with trastuzumab in a human prostate cancer xenograft model and underlying mechanisms. Legrier, M.-E.; Oudard, S.; Judde, J.-G.; Guyader, C.; de Pinieux, G.; Boye, K.; de Cremoux, P.; Dutrillaux, B.; Poupon, M.-F. Section Recherche, Institut Curie, Paris, Fr. British Journal of Cancer (2007), 96(2), 269-276. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 146:434377 AN 2007:81374 CAPLUS

Abstract

Antitumor activity of docetaxel (Taxotere) in hormone-dependent (HD) and hormone-independent (HID) prostate cancer PAC120 xenograft model was previously reported, and its level was assocd. with HER2 protein expression. In the present study, we evaluate the antitumor effects of docetaxel combined with trastuzumab (Herceptin), an anti-HER2 antibody. Although trastuzumab alone had no effect on tumor growth, it potentiated the antitumor activity of docetaxel in HD tumors and more strongly in HID variants. Using the HID28 variant, we show that docetaxel treatment of tumor-bearing mice induces an increased HER2 mRNA expression of the tyrosine kinase receptor of 25-fold 24 h after docetaxel treatment, while HER2 protein and p-AKT decreased. This was followed by an increase of HER2 protein 3 days (two-fold) after docetaxel treatment and by a strong HER2 release in the serum of treated mice; expression of phospho-ERK, p27, BCL2 and HSP70 concomitantly increased. Similar mol. alterations were induced by docetaxel plus trastuzumab combination, except for that there was a transient and complete disappearance of AR and HSP90 proteins 24 h after treatment. We show that in addn. to its known effects on tubulin and mitotic spindles, docetaxel induces complex signalization pathway mechanisms in surviving cells, including HER2, which can be pharmacol. targeted. This study suggests that the docetaxel/trastuzumab combination may prove an effective therapeutic approach for HER2-expressing hormone-refractory prostate cancer.

Answer 20:

Bibliographic Information

HER2 signaling modulates the equilibrium between pro- and antiangiogenic factors via distinct pathways: implications for HER2-targeted antibody therapy. Wen, X.-F.; Yang, G.; Mao, W.; Thornton, A.; Liu, J.; Bast, R. C., Jr.; Le, X.-F. Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. Oncogene (2006), 25(52), 6986-6996. Publisher: Nature Publishing Group, CODEN: ONCNES ISSN: 0950-9232. Journal written in English. CAN 146:26257 AN 2006:1153327 CAPLUS

Abstract

The authors detd. the impact of HER2 signaling on two proangiogenic factors, vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8), and on an antiangiogenic factor, thrombospondin-1 (TSP-1). Re-expression of HER2 in MCF-7 and T-47D breast cancer cells that endogenously express low levels of HER2 resulted in elevated expression of VEGF and IL-8 and decreased expression of TSP-1. Inhibition of HER2 with a humanized anti-HER2 antibody (trastuzumab, or Herceptin) or a retrovirus-mediated small interfering RNA against HER2 (siHER2) decreased VEGF and IL-8 expression, but increased TSP-1 expression in BT474 breast cancer cells that express high levels of HER2. These in vitro results were further evaluated by treatment of BT474 xenografts in immunosuppressed mice with trastuzumab. Trastuzumab inhibited growth of BT474 xenografts and decreased microvascular d. assocd. with downregulation of VEGF and IL-8 and with upregulation of TSP-1 expression. Inhibiting the PI3K-AKT pathway decreased VEGF and IL-8 expression. AKT1 overexpression increased VEGF and IL-8 expression, but did not increase TSP-1 expression. A p38 kinase inhibitor, SB203580, instead blocked TSP-1 expression and a p38 activator, MKK6, increased TSP-1 expression. Trastuzumab

stimulated sustained p38 activation and SB203580 attenuated the TSP-1 upregulation induced by trastuzumab. HER2 signaling thus influences the equil. between pro- and antiangiogenic factors via distinct signaling pathways. Trastuzumab inhibits angiogenesis and tumor growth, at least in part, via activation of the HER2-p38-TSP-1 pathway and inhibition of the HER2-PI3K-AKT-VEGF/IL-8 pathway.

Answer 21:

Bibliographic Information

Application and potential limitations of animal models utilized in the development of trastuzumab (Herceptin): A case study. Pegram, Mark; Ngo, Debbie. David Geffen School of Medicine, UCLA Center for the Health Sciences, University of California Los Angeles, Los Angeles, CA, USA. Advanced Drug Delivery Reviews (2006), 58(5-6), 723-734. Publisher: Elsevier B.V., CODEN: ADDREP ISSN: 0169-409X. Journal; General Review written in English. CAN 145:312426 AN 2006:876833 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The preclin. and clin. development of trastuzumab, a humanized monoclonal antibody directed against a juxtamembrane epitope in the HER2 receptor ectodomain, relied heavily on the use of animal models to validate HER2 as a potential MAb target. The identification of HER2 (neu) as a proto-oncogene was first established in a carcinogen-induced brain tumor in the rat. Transgenic mouse technol. led to an understanding of the role of HER2 in pathogenesis of breast cancer. Transfection studies of human HER2 cDNA into murine xenograft models further explored the role HER2 plays in tumor progression and metastasis. A murine subrenal capsule fresh human tumor explant assay was utilized to test efficacy of various murine monoclonal anti-HER2 antibodies, and the data were helpful in choosing the most efficacious for subsequent human engineering for clin. use. HER2-overexpressing xenograft models in athymic mice were used to test the efficacy of anti-HER2 antibodies, develop dose-response relationships, measure drug interactions between trastuzumab and chemotherapy, and optimize dosing schedules of chemotherapeutics combined with trastuzumab. In this work, we will highlight the utility of animal models exploited in the development of trastuzumab - noting not only their contribution to drug development but also their limitations in translation of preclin. data into the clinic. It is likely that the experience we gained in the case of preclin. animal models to study in vivo effects of trastuzumab have parallels in the development of other monoclonal antibodies since overcoming the species boundaries (i.e. cross-reactivity with antigenic determinant, development of cross-species neutralizing antibodies, and cross-species interaction with activating Fc receptors on immune effector cells) are major limitations in the design and interpretation of preclin./translational expts. designed to fulfill various regulatory requirements prior to initiation of phase I human clin. trials.

Answer 22:

Bibliographic Information

Antitumor Effect of Trastuzumab for Pancreatic Cancer with High HER-2 Expression and Enhancement of Effect by Combined Therapy with Gemcitabine. Kimura, Kenjiro; Sawada, Tetsuji; Komatsu, Midori; Inoue, Masafumi; Muguruma, Kazuya; Nishihara, Tamahiro; Yamashita, Yoshito; Yamada, Nobuya; Ohira, Masaichi; Hirakawa, Kosei. Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan. Clinical Cancer Research (2006), 12(16), 4925-4932. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:265942 AN 2006:816361 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The purpose of the present study was to evaluate whether trastuzumab has antitumor effect against pancreatic cancer and whether this effect is concordant with levels of HER-2, which is reportedly overexpressed in pancreatic cancer. We also investigated whether the effect is potentiated in combined therapy with gemcitabine. Exptl. Design: Using immunohistochem. and FACScan, we analyzed HER-2 expression in 16 pancreatic cancer cell lines. The in vitro antiproliferative effect of trastuzumab, alone and in combination with gemcitabine, was examd. by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The in vitro antibody-dependent cell-mediated cytotoxicity of trastuzumab was investigated by 51Cr release assay. The in vivo antitumor effect

of trastuzumab, alone and in combination with gemcitabine, was evaluated in nude mouse xenograft growth. The survival benefit was evaluated in a Capan-1 orthotopic implanted nude mouse model. RESULTS: HER-2 expression of 2+ or more was obsd. in 10 and of 3+ in 2 of the 16 cell lines. No in vitro growth-inhibitory effect of trastuzumab was found in any cell line, but trastuzumab induced antibody-dependent cell-mediated cytotoxicity in proportion to HER-2 expression level. Trastuzumab inhibited tumor growth in Capan-1 (HER-2: 3+) xenografts and prolonged survival in the orthotopic model. These effects were increased by combined therapy with gemcitabine. In contrast, trastuzumab exhibited no antitumor effect against PANC-1 (HER-2: 1+) or SW1990 (HER-2: 2+) xenografts. CONCLUSIONS: The antitumor effect of trastuzumab in pancreatic cancer with high HER-2 expression was shown in vitro and in vivo. Clin. application of trastuzumab is expected in pancreatic cancer with 3+ HER-2 expression.

Answer 23:

Bibliographic Information

Intraperitoneal immunotherapy for metastatic ovarian carcinoma: resistance of intratumoral collagen to antibody penetration. Choi, Jaehwa; Credit, Kimberly; Henderson, Karla; Deverkadra, Ravi; He, Zhi; Wiig, Helge; Vanpelt, Heather; Flessner, Michael F. Department of Medicine and Pathology, University of Mississippi Medical Center, Jackson, MS, USA. Clinical Cancer Research (2006), 12(6), 1906-1912. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:186650 AN 2006:264036 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Convective transport of macromols. from the peritoneal cavity into tumor is detd. by its hydraulic permeability and the pressure gradient. Previous studies showed that establishing a pressure gradient into the tumor failed to result in significant penetration. This study addresses the hypothesis that the extracellular matrix is the major resistance to the penetration of an i.p. injected antibody. Human ovarian tumors (SKOV-3 and OVCAR-3) were established in the abdominal wall of athymic rats. After anesthesia, the tumor serosal surface was treated for 2 h with Krebs soln. (control), collagenase (37.5 unit/mL), or hyaluronidase (10 unit/mL) followed by 3 h of convective delivery of radiolabeled IgG. Transport of antibody into the tumor was measured with quant. autoradiog. along with the tumor interstitial pressure, concn. of collagen and hyaluronic acid, and IgG vol. of distribution. Antibody was excluded from 42-53% of tumor extracellular vol. Exposure of tumors to hyaluronidase did not enhance IgG transport despite removal of 90% of the hyaluronan from the exposed tumor. In contrast, collagenase reduced collagen content, lowered tumor interstitial pressure, and markedly enhanced antibody penetration. Thus, redn. of collagen, but not hyaluronan, in the matrix of ovarian xenografts enhanced the transport of i.p. injected antibody. Although high interstitial pressure is a deterrent to convective transport of macromols. into the tumor parenchyma, the structure of the interstitial matrix provides an inherent resistance, which must be overcome before effective delivery of an antibody.

Answer 24:

Bibliographic Information

In vitro and in vivo Effects of Combination of Trastuzumab (Herceptin) and Tamoxifen in Breast Cancer. Wang, Chun-Xia; Koay, Debbie C.; Edwards, Andrea; Lu, Zhao; Mor, Gil; Ocal, Idris T.; DiGiovanna, Michael P. Departments of Internal Medicine (Section of Medical Oncology) and Pharmacology, Obstetrics and Gynecology, Pathology, and the Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA. Breast Cancer Research and Treatment (2005), 92(3), 251-263. Publisher: Springer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 144:68382 AN 2005:989330 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Extensive interactions between estrogen receptor α (ERα) and HER2 signaling pathways have been described. Using BT-474 human breast cancer cells, we have previously shown that the combination of tamoxifen (TAM) and Herceptin results in strong synergistic growth inhibition, enhancement of G0-G1 cell cycle accumulation, inhibition of HER2 activity and a cytostatic effect without cell death.

To further examine the underlying mechanism of synergy, we investigated the effect of this drug combination on ERα function and growth factor downstream signaling. TAM caused a small increase in ERα levels while Herceptin had no effect, and both drugs caused an increase in the level of Ser118-phosphorylated ERα. However, both TAM and Herceptin individually inhibited ERα transcriptional activity, although the combination did not have a greater effect than either single agent. Herceptin inhibited MAPK and Akt activity, while TAM had no effect on these either as a single agent or when added to Herceptin. Using a BALB/c athymic BT-474 in vivo xenograft model, the drug combination (Herceptin 0.3 mg/kg i.p. twice weekly, TAM 1.0 mg/mouse i.p. three times per wk) showed a greater inhibition of tumor growth compared to either single agent. Tumor exts. and fixed sections were examd. at the end of the treatment period for treatment-specific alterations: we noted a paradoxical proliferation-inducing effect of TAM that was reversed by the addn. of Herceptin. Our results indicate that combined targeting of both peptide growth factor receptors and ERα represents a promising breast cancer treatment strategy.

Answer 25:

Bibliographic Information

Suppression of tumor growth in human gastric cancer with HER2 overexpression by an anti-HER2 antibody in a murine model. Matsui, Yoko; Inomata, Masafumi; Tojigamori, Manabu; Sonoda, Kazuya; Shiraishi, Norio; Kitano, Seigo. Department of Surgery I, Oita University Faculty of Medicine, Oita, Japan. International Journal of Oncology (2005), 27(3), 681-685. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 144:5223 AN 2005:981567 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New modalities are necessary for the treatment of patients with unresectable gastric cancer. The aim of this study was to investigate whether or not anti-HER2 antibody could suppress the growth of human gastric cancer cells with HER2 overexpression in vitro and in vivo. Four human gastric cancer cell lines, NCI-N87, MKN-45P, Kato-III, and MKN-1, were used in this study. The suppression of cell proliferation in vitro and of s.c. tumor growth in a nude mouse model after treatment with trastuzumab was examd. The expression of HER2 protein was investigated by Western blot anal. The effect of trastuzumab on the survival rate of nude mice with peritoneal dissemination was examd. Trastuzumab significantly reduced proliferative activity in NCI-N87, a HER2-overexpressing human gastric cancer cell line, in vitro. In the nude mouse model with transplanted s.c. tumor, trastuzumab significantly suppressed the tumor growth of NCI-N87 cells, and then HER2 expression was reduced. Trastuzumab improved the survival rate of mice with peritoneal dissemination of MKN-45P cells. Trastuzumab therapy is a potential candidate for a novel treatment of HER2-overexpressing gastric cancer.

Answer 26:

Bibliographic Information

Gefitinib-trastuzumab combination on hormone-refractory prostate cancer xenograft. Formento, Patricia; Hannoun-Levi, Jean-Michel; Gerard, Francoise; Mazeau, Christiane; Fischel, Jean-Louis; Etienne-Grimaldi, M. C.; Gugenheim, Jean; Milano, Gerard. Oncopharmacology Unit, Centre Antoine Lacassagne, Nice, Fr. European Journal of Cancer (2005), 41(10), 1467-1473. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 143:339060 AN 2005:520841 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New drugs and new combinations of drugs have recently shown promising clin. activity in hormone refractory prostate cancer. We studied the assocn. of gefitinib with trastuzumab on the androgen-refractory prostate cancer cell line DU145 expressing both epidermal growth factor receptor (EGFR) and HER-2. Drug combinations with radiotherapy (RT) were considered along with the anal. of factors linked to cell proliferation and apoptosis. The antitumor effects of gefitinib were more pronounced than those obsd. with trastuzumab. In mice receiving the gefitinib-trastuzumab combination, redn. in tumor vol. was inferior to that predicted by the obsd. impact of the agents alone. The presence of trastuzumab markedly attenuated the relative increase on p27 expression and the Bax:Bcl2 ratio

induced by gefitinib. The combination gefitinib-RT had similar antitumor effects as those predicted by the impact of the individual treatments, whereas the effect of the trastuzumab-RT combination was inferior to that predicted by the individual effects. The present data should be borne in mind when designing new clin. schedules for treatment of hormone-refractory prostate cancer including the use of HER inhibitors.

Answer 27:

Bibliographic Information

Trastuzumab and Liposomal Doxorubicin in the Treatment of MCF-7 Xenograft Tumor-Bearing Mice: Combination Does Not Affect Drug Serum Levels. Waterhouse, Dawn N.; Denyssevych, Tetyana; Hudon, Norma; Chia, Stephen; Gelmon, Karen A.; Bally, Marcel B. BC Cancer Agency, USA. Pharmaceutical Research (2005), 22(6), 915-922. Publisher: Springer, CODEN: PHREEB ISSN: 0724-8741. Journal written in English. CAN 143:241449 AN 2005:506482 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose We assessed the combination of doxorubicin or liposomal doxorubicin with trastuzumab for alterations in peak serum drug levels, as these agents are increasingly being paired in the treatment of aggressive breast cancer. We hypothesized that trastuzumab would exhibit a slower rate of elimination from the serum when in combination with liposomal doxorubicin based on the known effects of liposomal doxorubicin on phagocytic cells of the mononuclear phagocyte system (MPS), which are responsible in part for the uptake and degrdn. of antibodies. Methods Doxorubicin and trastuzumab serum levels were assessed following injection of free doxorubicin, liposomal doxorubicin, or trastuzumab into female RAG2-M mice bearing s.c. MCF-7HER-2 tumors. The effects of combination drug treatment on tumor growth were compared to single-agent treatment. Results Peak serum trastuzumab levels were not altered as a result of addn. of doxorubicin therapy, nor were doxorubicin levels altered over 24 h as a result of coadministration of trastuzumab. Liposomal doxorubicin administration did result in serum doxorubicin levels 200- to 1000-fold higher than with injection of free doxorubicin. Conclusions For the specific combination of trastuzumab with doxorubicin, either in free or liposomal form, coadministered in mice, there was no impact of one drug on the other in terms of peak serum drug levels or efficacy.

Answer 28:

Bibliographic Information

Imaging of HER2/neu expression in BT-474 human breast cancer xenografts in athymic mice using [99mTc]-HYNIC-trastuzumab (Herceptin) Fab fragments. Tang, Ying; Scollard, Deborah; Chen, Paul; Wang, Judy; Holloway, Claire; Reilly, Raymond M. Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON, Can. Nuclear Medicine Communications (2005), 26(5), 427-432. Publisher: Lippincott Williams & Wilkins, CODEN: NMCODC ISSN: 0143-3636. Journal written in English. CAN 144:2299 AN 2005:336715 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: To evaluate the ability of trastuzumab (Herceptin) Fab, labeled with Tc through introduced hydrazinenicotinamide (HYNIC) functionalities, to image HER2/neu-overexpressing human breast cancer xenografts in athymic mice. Methods: Fab fragments were produced by immobilized papain digestion of trastuzumab IgG, followed by purifn. by ultrafiltration. The immunoreactivity of trastuzumab Fab was evaluated by receptor-binding assays against HER2/neu-pos. SK-BR-3 human breast cancer cells. Trastuzumab Fab fragments were labeled with Tc following modification with HYNIC N-hydroxysuccinimide ester. Biodistribution and tumor imaging studies were performed in athymic mice bearing s.c. HER2/neu-overexpressing BT-474 human breast cancer xenografts following i.v. injection of 1.1 or 25 MBq of [99mTc]-trastuzumab Fab (30 μg), resp. The specificity of tumor uptake was assessed by comparison with that of [99mTc]-labeled irrelevant anti-CD33 HuM195 Fab. Results: Trastuzumab Fab was pure and exhibited preserved immunoreactivity towards SK-BR-3 cells (Kd=1.6×10-8 M). Modification with HYNIC diminished its receptor-binding affinity fourfold. [99mTc]-trastuzumab Fab localized avidly and specifically in BT-474 xenografts, achieving a tumor uptake of 10.7% of the injected dose (ID) per g and a tumor to blood (T/B) ratio of 3:1 at 24 h. The tumor uptake and T/B ratio for [Tc]-trastuzumab Fab were

significantly higher than those for control [99mTc]-HuM195 Fab (2.6% ID · g-1 and 0.9:1, resp.; P<0.05). Tumors were imaged as early as 2 h post-injection of [99mTc]-trastuzumab Fab, but were more clearly visualized at 6 and 24 h post-injection. Conclusions: [99mTc]-HYNIC-trastuzumab Fab localized specifically in HER2/neu-overexpressing human breast cancer xenografts in athymic mice, allowing imaging of the tumors within the useful lifetime of the radionuclide.

Answer 29:

Bibliographic Information

Herceptin down-regulates HER-2/neu and vascular endothelial growth factor expression and enhances taxol-induced cytotoxicity of human Ewing's sarcoma cells in vitro and in vivo. Guan, Hui; Jia, Shu-Fang; Zhou, Zhichao; Stewart, John; Kleinerman, Eugenie S. Division of Pediatrics and Department of Pathology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2005), 11(5), 2008-2017. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:19402 AN 2005:206837 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have previously shown that high levels of HER-2/neu protein were overexpressed in human Ewing's sarcoma cells (TC71, SK-ES1) relative to normal human osteoblasts. The purpose of this study was to det. whether herceptin alone or in combination with chemotherapeutic agents could inhibit the growth of Ewing's sarcoma in vitro and in vivo. Western blot anal. showed that the protein levels of HER-2/neu were decreased following herceptin treatment. Cell growth was also inhibited by herceptin in a dose-dependent manner with an IC50 of 4 mg/mL in TC71 and SK-ES1 cell line, whereas human immunoglobin had no effect. Northern blot and ELISA showed the RNA expression and protein levels of vascular endothelial growth factor were also inhibited by herceptin treatment with no alteration in HIF-1α protein and topoisomerase IIα expression. Furthermore, Ewing's sarcoma tumor growth was significantly delayed by 100 mg/kg herceptin treatment in our Ewing's sarcoma xenograft mouse model. Combining taxol with herceptin resulted in additive cytotoxicity, whereas herceptin-etoposide, doxorubicin, and 9-nitrocamptothecin combinations did not. Taxol-herceptin enhanced growth inhibition in TC71 cells in vitro compared with either agent alone. Ewing's sarcoma growth was also delayed in vivo and mean tumor size was significantly lower in mice treated with herceptin plus taxol than in those receiving taxol or herceptin alone. These data suggest that herceptin in combination with taxol may be a therapeutic option in the treatment of Ewing's sarcoma.

Answer 30:

Bibliographic Information

Imaging of HER2/neu-positive BT-474 human breast cancer xenografts in athymic mice using 111In-trastuzumab (Herceptin) Fab fragments. Tang, Ying; Wang, Judy; Scollard, Deborah A.; Mondal, Hridya; Holloway, Claire; Kahn, Harriette J.; Reilly, Raymond M. Division of Nuclear Medicine, University Health Network, Toronto, ON, Can. Nuclear Medicine and Biology (2005), 32(1), 51-58. Publisher: Elsevier Inc., CODEN: NMBIEO ISSN: 0969-8051. Journal written in English. CAN 143:281716 AN 2005:108139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Trastuzumab (Herceptin) Fab were prepd. by digestion of intact IgG with immobilized papain, derivatized with diethylenetriaminepentaacetic acid (DTPA) and radiolabeled with 111In. The dissocn. const. (Kd) for binding of Fab to HER2/neu-pos. SK-BR-3 human breast cancer cells was two- to threefold higher than for intact IgG (14-36 vs. 8-14 nM). The binding affinity was not significantly decreased after DTPA derivatization (Kd=47 nM). 111In-trastuzumab Fab localized specifically in HER2/neu-pos. BT-474 human breast cancer xenografts in athymic mice with tumor uptake of 7.8±0.7% injected dose (ID)/g and tumor/blood ratio of 25.2±1.6 at 72 h postinjection compared with 2.7±0.7% ID/g and 7.0±0.9 for 111In-HuM195 anti-CD33 Fab (significantly different, P<.001). Small (3-5 mm in diam.) BT-474 tumors were imaged with 111In-trastuzumab Fab as early as 24 h postinjection.

Answer 31:

Bibliographic Information

Treatment of HER-2/neu overexpressing breast cancer xenograft models with trastuzumab (Herceptin) and gefitinib (ZD1839): drug combination effects on tumor growth, HER-2/neu and epidermal growth factor receptor expression, and viable hypoxic cell fraction. Warburton, Corinna; Dragowska, Wieslawa H.; Gelmon, Karen; Chia, Stephen; Yan, Hong; Masin, Dana; Denyssevych, Tetyana; Wallis, Anne E.; Bally, Marcel B. Departments of Advanced Therapeutics and Medical Oncology, British Columbia Cancer Agency, BC, Can. Clinical Cancer Research (2004), 10(7), 2512-2524. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:342990 AN 2004:290933 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purpose of this research was to assess the effects of single agent and combination treatment with trastuzumab and gefitinib on tumor growth and tumor microenvironment in two HER-2/neu overexpressing breast xenograft models, MDA-MB-435/LCC6HER-2 (LCC6HER-2; estrogen receptor neg.) and MCF-7HER-2 (estrogen receptor pos.). LCC6HER-2 and MCF-7HER-2 cells, both in tissue culture and xenografts grown in SCID-Rag 2M mice, were treated with trastuzumab and gefitinib, alone or in combination. The rate of tumor growth was detd. In addn., tumor HER-2/neu and epidermal growth factor receptor expression, cell viability, cell cycle distribution, and proportion of viable hypoxic cells were detd. by flow cytometric analyses of single tumor cell suspensions. Both tumor models were very sensitive to trastuzumab and moderately sensitive to gefitinib in vivo. The combination resulted in therapeutic effects, as judged by inhibition of tumor growth, which was greater (albeit not statistically significant) than that obsd. with trastuzumab administered as a single agent. Trastuzumab was effective in down-regulating HER-2/neu, and gefitinib mediated a redn. in epidermal growth factor receptor expression on tumor cells. In LCC6HER-2 tumors, trastuzumab significantly reduced tumor cell viability, which was not improved by the addn. of gefitinib. Gefitinib dramatically reduced the proportion of viable hypoxic cells in LCC6HER-2 and MCF-7HER-2 tumors. This effect was abrogated by the addn. of trastuzumab. Although in vivo efficacy studies in two HER-2/neu overexpressing breast xenograft models showed that the combination of trastuzumab and gefitinib was effective, analyses of various cellular parameters failed to reveal beneficial effects and argue that this drug combination may not be favorable.

Answer 32:

Bibliographic Information

Effect of trastuzumab for human esophageal cancer. Yamazaki, Masanao; Yamashita, Yoshito; Kubo, Naoshi; Ohira, Masaichi; Hirakawa, Kosei. Dept. of Surgical Oncology, Osaka City University Graduate School of Medicine, Japan. Gan to Kagaku Ryoho (2003), 30(11), 1780-1783. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 140:390043 AN 2003:962591 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects on esophageal cancer of monoclonal antibody trastuzumab, directed against the HER2 protein, were evaluated in this study. Immunohistochem. study showed that 90% (45/50) of esophageal cancer specimens expressed HER2 protein, and flow cytometric anal. showed that 4 kinds of human esophageal cancer cells (TT, TE2, TE6, TE10) expressed high levels of HER2 protein. Trastuzumab treatment (100-500 ng/mL) was not able to inhibit the growth of the all kinds of cancer cells, but the combination treatment of trastuzumab and peripheral mononuclear cells resulted in antibody dependent cell-mediated cytotoxicity (ADCC) against the cancer cells TE6 and TE10 in a dose dependent manner. I.p. injection of trastuzumab at 1 mg/body twice a week for 5 wk significantly inhibited the growth of mice-bearing xenografts of TE6 and TE10. Our results suggest that trastuzumab therapy is useful in the treatment of human esophageal cancer.

Answer 33:

Bibliographic Information

Trastuzumab in the treatment of HER2 positive breast cancer. Summerhayes, Maxwell. The Pharmacy Department, Guy's Hospital, London, UK. Journal of Oncology Pharmacy Practice (2001), 7(1), 9-25. Publisher: Arnold, Hodder Headline, CODEN: JOPPFI ISSN: 1078-1552. Journal; General Review written in English. CAN 137:41199 AN 2002:429802 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The aim of this study was to provide a comprehensive review of the preclin. and clin. pharmacol. and toxicol. of the monoclonal antibody trastuzumab, with particular ref. to its use in its approved indication, HER2/neu-overexpressing breast cancer. A MEDLINE search was conducted using the terms "trastuzumab" and "Herceptin" for the period 1995-2001. The ref. lists from retrieved articles were reviewed and other relevant papers identified. The abstr. books from the annual meetings of the American Society of Clin. and Oncol. and the European Society of Medical Oncol. were also reviewed. The aim of the review was to be comprehensive and descriptive. All studies contg. information deemed to be of interest were reviewed by the author; none were excluded on grounds of quality. Trastuzumab is a chimeric monoclonal antibody with a hypervariable region of murine origin inserted into a human IgG1 skeleton. Trastuzumab recognizes p185HER2/neu, the 185-kDa product of the HER2/neu protooncogene. This gene is overexpressed in around 20% of breast cancers and encodes for a transmembrane protein that has extensive structural homol. with the EGFR. HER2/neu overexpression is prognostic of short relapse-free and overall survival and, possibly, of poor response to certain hormonal and cytotoxic treatments. Trastuzumab inhibits the growth of HER2/neu-overexpressing tumor cells grown in tissue culture or as xenografts in mice. It also potentiates the action of certain cytotoxic drugs against such cells. These properties stimulated clin. trials of trastuzumab in women with HER2/neu-pos. breast cancer. Used alone, in women with heavily pretreated HER2/neu-pos. breast cancer, trastuzumab stabilized disease in 35% of cases and induced regression in a further 22%. Its use was assocd. with prolonged stabilization of quality of life.

When used in combination with paclitaxel, or anthracycline-based chemotherapy, as a first-line treatment for metastatic breast cancer, it increased response rates, time to disease progression and survival. Unfortunately, when used in conjunction with anthracyclines, trastuzumab has been assocd. with an unacceptable incidence of cardiotoxicity. For this reason, it is currently approved for use alone or in combination with paclitaxel. When added to paclitaxel as a first-line treatment, it increased the median time to disease progression from 3.0 to 6.9 mo (P=0.0001) and the 1-yr survival rate from 62% to 73%, with little toxicity except occasional and, generally, mild infusion reactions.

Answer 34:

Bibliographic Information

Trastuzumab in the treatment of non-small-cell lung cancer. Azzoli, Christopher G.; Krug, Lee M.; Miller, Vincent A.; Kris, Mark G.; Mass, Robert. Department of Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Seminars in Oncology (2002), 29(1, Suppl. 4), 59-65. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 137:272635 AN 2002:306004 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Trastuzumab is a humanized monoclonal antibody that binds to human epidermal growth factor-2 (HER2) and is approved by the US Food and Drug Administration for the treatment of advanced breast cancer that overexpresses HER2/neu protein. Preclin. data suggests a role for Trastuzumab in the treatment of non-small-cell lung cancer (NSCLC). HER2 protein is overexpressed in 20-66% of resected NSCLC tumors, and has been shown to predict poor patient outcome in multiple series. Expts. with NSCLC cell lines show that HER2 overexpression increases chemoresistance, invasiveness, and metastatic potential of the cells. In mouse xenograft expts., Trastuzumab halts tumor growth and is synergistic with cytotoxic chemotherapy. Ongoing phase II trials are showing that Trastuzumab can be added to std. chemotherapy in the treatment of patients with advanced NSCLC without addnl. toxicity, and with promising efficacy. Whether Trastuzumab will show a clear benefit for patients with NSCLC, either alone or in combination with established chemotherapy, remains to be proven in phase III testing.

Answer 35:

Bibliographic Information

Trastuzumab and chemotherapeutics: Drug interactions and synergies. Pegram, Mark D.; Lopez, Angela; Konecny, Gottfried; Slamon, Dennis J. Division of Hematology/Oncology, University of California Los Angeles, Los Angeles, CA, USA. Seminars in Oncology (2000), 27(6, Suppl. 11), 21-25. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 135:146958 AN 2001:155744 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previous studies have shown a synergistic interaction between trastuzumab (Herceptin; Genentech, Inc, South San Francisco, CA) and the cytotoxic drug cisplatin in human breast cancer cells. To define the nature of the interaction between trastuzumab and other classes of cytotoxic drugs, we applied multiple drug effect/combination index isobologram anal. to a variety of chemotherapeutic drug/trastuzumab combinations in vitro. Synergistic interactions at clin. relevant drug concns. were obsd. for trastuzumab in combination with cisplatin, docetaxel, thiotepa, 4-OH cyclophosphamide, vinorelbine, and etoposide. Additive cytotoxic effects were obsd. with trastuzumab plus doxorubicin, paclitaxel, methotrexate, and vinblastine. One drug, 5-fluorouracil was antagonistic with trastuzumab in vitro. In vivo drug/trastuzumab studies were conducted with HER-2/neu-transfected MCF7 human breast cancer xenografts in athymic mice. Combinations of trastuzumab plus cisplatin, docetaxel, cyclophosphamide, doxorubicin, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant redn. in xenograft vol. compared to chemotherapy-alone controls ($P < .05$). The synergistic interaction of trastuzumab with specific chemotherapeutic agents suggests rational combinations for testing in human clin. trials.

Answer 36:

Bibliographic Information

Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). Sliwkowski, Mark X.; Lofgren, Julie A.; Lewis, Gail D.; Hotaling, Timothy E.; Fendly, Brian M.; Fox, Judith A. Genentech, Inc, South San Francisco, CA, USA. Seminars in Oncology (1999), 26(4, Suppl. 12), 60-70. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal; General Review written in English. CAN 132:136046 AN 1999:620138 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review with 75 refs. HER2 is a ligand-less member of the human epidermal growth factor receptor or ErbB family of tyrosine kinases. In normal biol. systems, HER2 functions as a co-receptor for a multitude of epidermal growth factor-like ligands that bind and activate other HER family members. HER2 overexpression is obsd. in a no. of human adenocarcinomas and results in constitutive HER2 activation. Specific targeting of these tumors can be accomplished with antibodies directed against the extracellular domain of the HER2 protein. One of these antibodies, 4D5, has been fully humanized and is termed trastuzumab (Herceptin; Genentech, San Francisco, CA). Treatment of HER2-overexpressing breast cancer cell lines with trastuzumab results in induction of p27KIPI and the Rb-related protein, p130, which in turn significantly reduces the no. of cells undergoing S-phase. A no. of other phenotypic changes are obsd. in vitro as a consequence of trastuzumab binding to HER2-overexpressing cells. These phenotypic changes include down-modulation of the HER2 receptor, inhibition of tumor cell growth, reversed cytokine resistance, restored E-cadherin expression levels, and reduced vascular endothelial growth factor prodn. Interaction of trastuzumab with the human immune system via its human IgG1 Fc domain may potentiate its antitumor activities. In vitro studies demonstrate that trastuzumab is very effective in mediating antibody-dependent cell-mediated cytotoxicity against HER2-overexpressing tumor targets. Trastuzumab treatment of mouse xenograft models results in marked suppression of tumor growth. When given in combination with std. cytotoxic chemotherapeutic agents, trastuzumab treatment generally results in statistically superior antitumor efficacy compared with either agent given alone.

Taken together, these studies suggest that the mechanism of action of trastuzumab includes antagonizing the constitutive growth-signaling properties of the HER2 system, enlisting immune cells to attack and kill the tumor target, and augmenting chemotherapy-induced cytotoxicity.